REMARKS

Claims 104-119 presently appear in this case. Claims 112-119 have been withdrawn from consideration. No claims have been allowed. The official action of February 20, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a polypeptide that binds to NIK, which is the intracellular domain of cγc or a fragment, variant, salt or functional derivative thereof that binds to NIK. The invention also relates to the corresponding DNA, vectors and cells containing such DNA, a method for the production of the polypeptide using such DNA, and antibodies that specifically recognize such polypeptides.

The examiner has maintained the restriction requirement on the ground that the originally presented claims lacked a special technical feature and, thus, lacked unity and therefore the requirement is still deemed proper and is therefore made final. This refusal to reconsider the restriction requirement in light of the amended claims is respectfully traversed.

The examiner is apparently taking the position that amendments to the claims made after filing of the case, but prior to examination on the merits may be totally disregarded

when considering unity of invention. It is respectfully submitted, however, that there is no justification for such an action in the MPEP or in the Guidelines with respect to unity of invention put out by the PCT. It is not understood why the examiner considers that a unity of invention requirement is set in stone and cannot be revised in light of amendments to the claims made with an election and prior to examination. Respectfully, the amendments to the claims and the arguments why the unity of invention requirement no longer applies to the amended claims cannot be simply disregarded. Reconsideration of the requirement for the reasons set forth in applicant's response of November 16, 2006, as supplemented on December 4, 2006, is again respectfully urged.

It is noted that the statements in paragraph 2 of the official action are inconsistent with the statements in paragraph 1 and in the office action summary on page 1 of the official action. It is apparent that claims 104-111 are considered to be in Group II and are being examined on the merits.

The examiner states that the use of the trademark "Clontech" on page 47 has been noted. The examiner states that it should be capitalized whenever it appears and be accompanied by the generic terminology.

The term "Clontech" as used on page 47 is not a trademark. It is the trade name of the company from which the vector was obtained or from which the assay was obtained. As the word is not a trademark and it is not being used in a trademark sense on page 48, reconsideration and withdrawal of this statement of the examiner is respectfully urged. Any true trademarks noted in the specification have now been capitalized. If the examiner notices any others that are definiately trademarks, it is respectfully requested that they be brought to applicant's attention for any correction that may be necessary.

The specification has also otherwise been carefully reviewed and amended to correct errors in terminology, grammar, punctuation and spelling.

Claims 104-107 have been rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The examiner states that the claims read on the naturally occurring intracellular domain of a cγc polypeptide that binds to NIK. As such, the examiner states that the claims are directed to non-statutory subject matter. The examiner states that this rejection may be overcome by narrowing the claims to encompass only isolated or purified polypeptides with the desired activity that do not read on

naturally occurring subject matter. This rejection is respectfully traversed.

Claim 104 has now been amended to change the preamble to read "consisting of" rather than "comprising." The "wherein" clause at the end has also been removed in light of the new matter rejection, which will be discussed below. It is clear that the presently amended claims do not read on a product of nature because a polypeptide consisting of the intracellular domain of cγc does not exist in nature. The intracellular domain only exists as part of the entire receptor. The claims do not read on the entire receptor that is a product of nature. Accordingly, as the claims do not read on a product of nature, it is not necessary to use the terms "isolated" or "purified." Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 104-107 have been rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The examiner states that, while the specification is enabling for a peptide consisting of residues 329-369 of SEQ ID NO:22 that binds to NIK, it does not reasonably provide enablement for the claimed genus of polypeptides. The examiner concedes that the level of skill of those in the art is high. The examiner states that there are four working models of polypeptides that bind to NIK in the specification. However, as will be discussed

below, this analysis is incorrect. There are many more working examples. The examiner cites an example of VEGF and PDGF that do not have the same properties. However, this is not the case with the present application that deals only with binding properties and in which the variants can only differ by no more than four amino acids, as will be discussed below. The examiner concedes that guidance is given regarding how to make and test variants of any protein. The examiner states that the claims are excessively broad and erroneously states that the specification does not provide any guidance on which portion of the 85 or so residues from the intracellular domain portion of SEQ ID NO:2 are required in order to bind to NIK. The examiner considers it to be entirely unpredictable that a salt of a binding peptide would still bind or a functional derivative of a binding peptide would still bind. The examiner erroneously states that none of the examples teach variants with at least 90% identity. As will be discussed below, at least five such variants are disclosed in the specification. Finally, the examiner concludes that, due to the large quantity of experimentation necessary to determine which polypeptides are capable of binding to NIK, undue experimentation would be required to make and/or use the claimed invention in its full scope. This rejection is respectfully traversed.

In order to reduce the amount of experimentation that would be necessary in order to practice the full scope of the present claims, claim 104 has now been amended to specify that the polypeptide consists of the intracellular domain of cγc, a fragment thereof that retains the ability to bind to NIK, or a variant of the intracellular domain or fragment that maintains at least 95% identity therewith and retains the ability to bind NIK. The polypeptide can also be a salt or functional derivative of any of these. The functional derivative must be an ester or aliphatic amide of a carboxyl group of the polypeptide or an N-acyl derivative of a free amino group of the polypeptide or an O-acyl derivative of a free hydroxyl group of the polypeptide. It would not take undue experimentation to determine every fragment or variant of the intracellular domain of cγc that retains the ability to bind to NIK. While molecular biology is admittedly an unpredictable art, the skill in the art is very high. Furthermore, the present specification discloses the sequences of many fragments and variants that maintain the ability to bind to NIK. These include 41 MDD, which is residues 329-369 of cγc; 44 MPD, which is 282-325 of cγc; ICDcγc, which is amino acids 289-369 of cγc; the fragment 289-325 of cγc, and the variants of 289-369 including PP336,337AA; PP360,361AA; K338A;

E344A; and W358A. All of these bind to NIK, although some bind more strongly than others.

The present specification contains assays for determining binding, including the yeast two-hybrid assay and immunoprecipitation assays. The specification discloses how to obtain fragments and make mutations. Furthermore, the specification teaches what parts of the sequence are most important for binding. Note in particular the importance of the C-terminal 41 amino acids and particularly the prolines at 360 and 361.

The examiner's attention is invited to *Ex parte Kubin*, 2007 Pat. App. LEXIS 13, May 31, 2007, which is a precedential opinion of the PTO Board of Patent Appeals and Interferences. A copy of this decision is attached hereto. It is also available on the PTO website under the list of Board precedential decisions. In *Kubin*, the claim under consideration was directed to an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to a certain amino acid sequence of 200 residues. Enablement and written description rejections were considered. With respect to the enablement rejection, the Board stated at pages 20-21:

> The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to

> do so were well known to those skilled in the art. … A "patent need not teach, and preferably omits, what is well known in the art." … Thus, we conclude the Specification would have enabled the full scope of claim 73.

As discussed above, the present specification contains substantial detail and many examples, much more so than in the *Kubin* specification. Furthermore, the present variants are limited to 95% identity, while in *Kubin* the Board held that even 80% identity was sufficiently enabled, i.e., would not involve undue experimentation. Thus, for the same reasons that the enablement rejection was overturned in *Kubin*, the enablement rejection must be withdrawn here. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 22-31 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The examiner states that the factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The examiner states that a description

of a genus may be achieved by means a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. The examiner states that there are four species of the claimed genus disclosed that are within the scope of the claimed genus, including 41 MDD, 44 MPD, 1-357 and 1-341. The examiner states that the specification fails to provide an adequate description of specific structural and functional limitations for the claimed genus of polypeptides, fragments, variants, salts or functional derivatives and that in the absence of sufficient recitation of distinguishing characteristics the specification does not provide adequate written description of the genus. This rejection is respectfully traversed.

The present claims have now been amended to specify that the variants must maintain 95% identity to the intracellular domain of cγc or functional fragment thereof. The intracellular domain of cγc has 86 amino acids (residues 284-369 of SEQ ID NO:22); 95% of 86 is 82. Thus, the claims only allow a maximum of four amino acid changes. With respect to variants of fragments, the number of amino acids that can be varied will be reduced depending on the size of the fragment. Thus, an NIK binding fragment of the intracellular

domain of cγc having 20 amino acids would only permit a variation of 1 amino acid, and that variant must also bind NIK. This is a relatively modest genus.

Furthermore, the present specification contains very substantial guidance as to what parts of this relatively small polypeptide may be varied and still retain binding capability. Thus, it discloses that there is a binding domain at 329 to 369 and there is another binding domain at 282 to 325. See Table 2 for the 41 MDD polypeptide (cγc 329-369) and page 49, line 12, to page 50, line 3, with respect to 44 MDP (cγc 282-325). Table 1 also shows that in experiments with almost the entirety of the intracellular domain (cγc 289-369), i.e., all but five amino acids thereof, this polypeptide binds strongly to NIK. Furthermore, Table 1 shows that the fragments at cγc 289-357 and 289-325 also bind. Accordingly, there is substantial guidance as to what portions of the sequence are needed for a strong binding or for binding at all, which is evidence that applicants were in possession of the full scope of the invention.

As to variants, the examiner's attention is invited to Table 3 of the present specification that shows five different variants that bind to NIK, including cγc 289-369 (PP336, 337AA); cγc 289-369 (PP360, 361AA); cγc 289-369

(K338A); cγc 289-369 (E344A); and cγc 289-369 (W358A). While the PP360,361AA variant still bound, its degree of binding was substantially decreased, showing the importance of the prolines at 360 and 361 to the binding capability at least of the 41 MDD fragment. This substantial number of examples and the guidance given to those of ordinary skill in the art are all evidence that applicant was in possession of the modest scope presently being claimed.

In *Ex parte Kubin*, discussed above, the Board held that a claim directed to a polypeptide of at least 80% identity to a specific sequence and that has certain binding properties did not meet the written description requirement. However, that is not to say that the same logic would apply to the much narrower claims of the present application. Not only are the claims of *Kubin* directed to polypeptides at least 80% identical to the underlying sequence, but the underlying sequence is much longer. It is a sequence of 200 amino acids and the *Kubin* claim would permit a variation of 40 amino acids. That is quite different from the present claims that allow a variation of a maximum of only four amino acids. In *Kubin*, appellants had sequenced only two nucleic acids falling within the scope of the claim, none of which varied the amino acids of the underlying sequence and, thus, the Board did not consider these sequences to be representative of the genus.

To the contrary, the present application has many examples, as listed above, including five examples that vary amino acids of the underlying sequence. These sequences are representative of the genus, particularly in light of the disclosure of the structural features common to the members of the genus, i.e., the particular binding domains and the important amino acids. In *Kubin* the Board specifically stated that the specification does not describe what domains of the sequences are correlated with the required binding. This is in distinction to the present application where the binding domains are specifically disclosed. In *Kubin* the Board specifically noted that the specification did not describe which of the amino acids could be varied and still maintain binding. In the present case, however, there is substantial disclosure of variations of amino acids and still retaining binding.

The Board specifically considered hypothetical Example 14 in the PTO's "Synopsis of Application of Written Description Guidelines available at www.uspto.gov/web/patents/guides.htm. The Board stated that compliance with the written description requirement is essentially a fact based inquiry that will necessarily vary depending on the nature of the invention claimed. It also stated that the hypothetical examples of the Synopsis can be helpful in understanding how to apply the relevant law but

they do not create a rigid test. In this case, however, the facts are substantially identical to the facts in the hypothetical example and *Kubin* provides no reason why that example must be discarded.

The claim in hypothetical example 14 also recites variants that are at least 95% identical to the underlying sequence and possess a particular function. In that analysis, however, the specification disclosed only the underlying sequence and no variants at all. The analysis in the Synopsis concluded:

> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the referenced sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Thus, the conclusion was reached in that hypothetical example that the disclosure meets the requirements of 35 U.S.C. 112, first paragraph, as providing adequate written description for

the claimed invention. As discussed above, this hypothetical example is substantially different from the extremely broad genus of 80% identity to a 200 amino acid SEQ ID NO. While 80% identity may not meet the written description requirement, 95%, which in this case amounts to no more than four variations, is, according to the Synopsis example 14, sufficiently similar to the single species disclosed as to allow one of ordinary skill in the art to conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus. How much more so must the present situation be considered to be in compliance with the written description requirement, where there are many more than one example and specific disclosure is present as to the necessary common structural attributes that would be possessed by all the members of the genus.

The Board did not say that the reasoning of the Synopsis example 14 was no longer applicable. It only said that every case must be decided on its own facts and in the facts of *Kubin* there was no written description. It is urged, however, that under the present facts, there is adequate written description for the exact reasons set forth in the analysis of Example 14, discussed above. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 104-107 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that this is in the nature of a new matter rejection. The examiner states that there is no description or disclosure in the specification to support the negative limitation in the "wherein" clause of claim 104, which specifically limits the polypeptide to no more of the cγc sequence than the intracellular domain thereof.

Claim 104 has now been amended to delete this clause that the examiner considers to be new matter. Accordingly, this rejection has now been obviated.

Claims 104-107 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The examiner states that the claims recite the functional requirement for being "capable of binding to NIK" and the examiner states that the metes and bounds of this language are undefined.

The examiner is requested to provide an example of a peptide that would be capable of binding to NIK, but that does not bind to NIK, so that this kind of rejection can be understood. Nevertheless, claim 104 has now been amended to change "capable of binging" to read "that binds." The examiner stated that with the previous language the claim was not limited to polypeptides that actually bind NIK. It is

believed that the new language now requires that the peptides actually bind NIK. This amendment should now obviate the indefiniteness rejection. Reconsideration and withdrawal thereof is therefore respectfully urged.

Claim 104 has been rejected under 35 U.S.C. 102(b) as being anticipated by Rothe. The examiner states that Rothe teaches peptide based substrate inhibitors of NIK including PKI and staurosporine. The examiner states that these compounds fall within the scope of a functional derivative of a variant of a fragment of SEQ ID NO:22. This rejection is respectfully traversed.

Claim 104 has now been amended to specfy that the functional derivative must be an ester or aliphatic amide of a carboxyl group of the polypeptide or an N-acyl derivative of a free amino group of a polypeptide or an O-acyl derivative of a free hydroxyl group of the polypeptide. All this is supported by the definition of "functional derivative" at page 23, in the paragraph beginning at line 13. Furthermore, the term "comprising" has been changed to read "consisting of" in the preamble. Furthermore, a double serine residue is not a fragment that retains the ability to bind NIK. Thus, in no event could the totally different peptides of Rothe anticipate the present claims. However, with the present amendment of the claims, Rothe certainly cannot be considered to anticipate

under any interpretation. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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